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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/057,776	01/25/2002	Kurt Berlin	81796	9632

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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	

DATE MAILED: 03/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/057,776	BERLIN, KURT	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is responsive to the Amendment received on November 24, 2004.

Preliminary Remark

The Office acknowledges the addition of claim 14.

Claim Rejections - 35 USC § 112

The rejection of claim 13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on July 28, 2004 is withdrawn in view of the Amendment received on November 24, 2004, amending the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1-3, 6-10, 12, and 13 under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), made in the Office Action mailed on July 28, 2004 is maintained for the reasons of record.

Applicants' arguments received on November 24, 2004 have been fully considered but they are not found persuasive for the following reasons.

Applicants' arguments are addressed in the same order they were received.

Applicants contend that the method of Gozalgo et al. does not involve amplification of the genomic DNA sample ***using*** fluorescently labeled *dinucleotides* (page 9, 2nd paragraph, Response).

If Applicants are contending that the instantly claimed invention employs labeled dinucleotides (two mononucleotide joined adjacently) as it is conventionally understood in the art, then Applicants are advised that neither the claimed method employs dinucleotides. The claims require the addition of either fluorescently labeled dCTP or dGTP (see claims 1 and 14).

For the purpose of argument, it is assumed that Applicants mean that the method involves the detection of fluorescently labeled dinucleotides (not *use* of fluorescently labeled dinucleotides).

Applicants also contend that Gonzalgo et al. not only employ radioactive markers for their detection instead of fluorescently labeled markers, but the radioactive marker is incorporated after the amplification of the genomic DNA has already been performed.

This argument is not found persuasive because had Gonzalgo et al. taught all of the claimed limitations as stated by Applicants, such art would have been rejected under a different statue, namely under 35 U.S.C. 102(b).

The teachings of Gonzalgo et al. relied upon is the steps of:

(a) treating a genomic DNA sample with bisulfite to convert non-5'-methylated cytosines to uracils while not converting the 5'methylated cytosines; and

(b) amplification of the resulting genomic DNA sample.

Gonzalgo et al. analyzes and separates the amplified product via electrophoresis (page 5, line 24).

Gonzalgo et al., however, in the detection of the CpG, employs methylation-sensitive single nucleotide primer extension (Abstract).

Yurov et al. and Davis et al. disclose a well-known method of amplifying and detecting target nucleic acid sequences via use of fluorescently labeled nucleotides, Cy3 and/or Cy5 (column 19, lines 18-20, Davis et al.) as well as the advantage of using Cy3 or Cy5 labels rather than other fluorescent labels:

"Cyanine dyes are also useful as fluorescent labels or biological macromolecules. Cyanine 3 dye provides ***significantly brighter fluorescence*** than any other fluorophore, including fluorescein..." (page 391, 1st column, Yurov et al.)

The use of fluorescently labeled nucleotides in generating target amplicons is well-known and practiced in the art of nucleic acid detections. Such teachings are prevalent, such as Affymetrix GeneChip™ which amplifies target nucleic acid sequences via use of fluorescently labeled nucleotides, followed by their hybridization to an array of immobilized probes.

Therefore, one of ordinary skill in the art at the time the invention was made would have had been reasonably motivated to modify the teachings of Gonzalgo et al. to employ the fluorescent labeled nucleotides for the detection of bisulfite treated genomic DNA.

Claims 4 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), as applied to claims 1-3, 6-10, 12, and 13 above, and

further in view of Apffel et al. (U.S. Patent No. 6,379,889 B1, issued April 30, 2002, filed November 4, 1999) and Roche et al. (Biotechnology Progress, 1997, vol. 13, pages 659-668).

Claims are drawn to a method of quantitating the methylation of cytosine bases in a DNA sample wherein the separation of the PCR products is achieved by either High Performance Liquid Chromatography (HPLC) or Capillary Gel Electrophoresis (CGE).

The teachings of Gonzalgo et al. Yurov et al. and Davis et al. have already been discussed above.

Gonzalgo et al., Yurov et al. and Davis et al. do not explicitly disclose the use of HPLC or CGE for PCR product separation.

Apffel et al. disclose a method of using HPLC for the separation of PCR amplicons from a PCR reaction mixture (column 3, lines 45-48)

Roche et al. disclose a method of using GCE for the separation of PCR amplicons (pp. 663, 2nd column bottom).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to expand the teachings of Gonzalgo et al., Yurov et al. and Davis et al. with the teachings of Apffel et al. and Roche et al. to arrive at the invention as claimed per suggestion offered by Gonzalgo et al., wherein the artisans state:

"There are many chromatographic techniques that can be used to isolate PCR amplification products (*or amplicons*)" (pp. 8, line 7-9).

One of ordinary skill in the art at the time the invention was made would have recognized various chromatographic techniques for separation/purification and the advantage offered by such techniques, as illustrated by Apffel et al. and Roche et al.:

"CE is capable of rapid, automated, reproducible, and high-resolution separation of small volumes of complex mixtures." (pp. 659, 2nd column; pp. 664, 1st column, *Roche*).

"Distinguish individual PCR amplicons (also referred to as PCR products herein) from a PCR reaction mixture." (column 3, lines 44-47).

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the teaching of Gonzalgo et al., Yurov et al. and Davis et al. given their explicit statement of feasibility to realize the advantages offered by the separation techniques of Apffel et al. and Roche et al. with a reasonable expectation of success.

Therefore, the invention as claimed is obvious over the cited references.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998), as applied to claim 1 above, and further in view of of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082).

The teachings of Gonzalgo et al., Yurov et al., and Davis et al. have been set forth above.

Gonzalgo et al., Yurov et al., and Davis et al. do not explicitly disclose that the amplification was multiplexed.

Wang et al. disclose a method of SNP genotyping which involves multiplex amplification from a genomic DNA via plurality of primers (pp. 1080). Wang et al. multiplexes 46 loci from a genomic DNA (pp. 1080, 3rd column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Gonzalgo et al., Yurov et al., and Davis et al. with the teachings and advantages disclosed by Wang et al. to arrive at the invention as claimed for the following reason.

Wang et al. clearly suggest the well-known advantage of multiplexing PCR reactions:

"We next sought to ***decrease substantially the sample preparation*** required to genotype large numbers of SNPs, as required to perform a genomic scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction." (page 1080, 3rd column).

One of ordinary skill in the art, therefore, would have been motivated to employ the well-known multiplex-PCR technique into the method disclosed by Gonzalgo et al., Yurov et al., and Davis et al. for the well-known advantage of reducing the sample preparation/contamination with a reasonable expectation of success.

Therefore, the invention as claimed is obvious over the cited references.

Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Gonzalgo et al. (WO 98/56952, published December 17, 1998) in view of Yurov et al. (Human Genetics, 1996, vol. 97, pages 390-398) and in light of Davis et al. (U.S. Patent No. 6,046,002, issued April 4, 2000, filed January 5, 1998).

Applicants' arguments received on November 24, 2004 have been fully considered but they are not found persuasive for the following reasons.

Applicants' arguments are addressed in the same order they were received.

Applicants contend that the method of Gozalgo et al. does not involve amplification of the genomic DNA sample ***using*** fluorescently labeled *dinucleotides* (page 9, 2nd paragraph, Response).

If Applicants are contending that the instantly claimed invention employs labeled dinucleotides (two mononucleotide joined adjacently) as it is conventionally understood in the art, then Applicants are advised that neither the claimed method employs dinucleotides. The claims require the addition of either fluorescently labeled dCTP or dGTP (see claims 1 and 14).

For the purpose of argument, it is assumed that Applicants mean that the method involves the detection of fluorescently labeled dinucleotides (not *use* of fluorescently labeled dinucleotides).

Applicants also contend that Gonzalgo et al. not only employ radioactive markers for their detection instead of fluorescently labeled markers, but the radioactive marker is incorporated after the amplification of the genomic DNA has already been performed.

This argument is not found persuasive because had Gonzalgo et al. taught all of the claimed limitations as stated by Applicants, such art would have been rejected under a different statue, namely under 35 U.S.C. 102(b).

The teachings of Gonzalgo et al. relied upon is the steps of:

(a) treating a genomic DNA sample with bisulfite to convert non-5'-methylated cytosines to uracils while not converting the 5'methylated cytosines; and

(b) amplification of the resulting genomic DNA sample.

Gonzalgo et al. analyzes and separates the amplified product via electrophoresis (page 5, line 24).

Gonzalgo et al., however, in the detection of the CpG, employ methylation-sensitive single nucleotide primer extension (Abstract).

Yurov et al. and Davis et al. disclose a well-known method of amplifying and detecting target nucleic acid sequences via use of fluorescently labeled nucleotides, Cy3 and/or Cy5 (column 19, lines 18-20, Davis et al.) as well as the advantage of using Cy3 or Cy5 labels rather than other fluorescent labels:

"Cyanine dyes are also useful as fluorescent labels or biological macromolecules. Cyanine 3 dye provides ***significantly brighter fluorescence*** than any other fluorophore, including fluorescein..." (page 391, 1st column, Yurov et al.)

The use of fluorescently labeled nucleotides in generating target amplicons is well-known and practiced in the art of nucleic acid detections. Such teachings are prevalent, such as Affymetrix GeneChip™ which amplifies target nucleic acid sequences via use of fluorescently labeled nucleotides, followed by their hybridization to an array of immobilized probes.

Therefore, one of ordinary skill in the art at the time the invention was made would have had been reasonably motivated to modify the teachings of Gonzalgo et al. to employ the fluorescent labeled nucleotides for the detection of bisulfite treated genomic DNA.

With regard to the method being "consisting of" the recited steps (a) through (d), the invention as claimed is determined to be obvious as one of ordinary skill in the art at the time the invention was made, when combined with the teachings of Gonzalgo et al., Yurov et al., and Davis et al. would have arrived at the method of the recited steps.

Double Patenting – Maintained

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

The provisional rejection of claims 1-13 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-29 of copending Application No. 10/220,090, made in the Office Action mailed on July 28, 2004 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Applicants' request received on November 24, 2004 to hold the rejection in abeyance has been fully considered but they are not found persuasive for the following reasons.

MPEP 804(I)(B), in instructing double patenting rejections between two co-pending applications, states:

> "If the "provisional" double patenting rejections in both applications ***are the only rejections remaining*** in those applications, the examiner should then ***withdraw that rejection*** in one of the applications (e.g., ***the application with the earlier filing date***) and permit the application ***to issue*** as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented."

However, the instant application has a rejection that is substantive other than the provisional double patenting rejection, and is therefore, maintained.

Claims 1-13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-26 of copending Application No. 10/220,896 made in the Office Action mailed on July 28, 2004 is maintained for the reasons of record. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Applicants' request received on November 24, 2004 to hold the rejection in abeyance has been fully considered but they are not found persuasive for the following reasons.

MPEP 804(I)(B), in instructing double patenting rejections between two co-pending applications, states:

> "If the "provisional" double patenting rejections in both applications ***are the only rejections remaining*** in those applications, the examiner should then ***withdraw that rejection*** in one of the applications (e.g., ***the application with the earlier filing date***) and permit the application ***to issue*** as a patent. The examiner should maintain the double patenting rejection in the other application as a "provisional" double patenting rejection which will be converted into a double patenting rejection when the one application issues as a patent. This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented."

However, the instant application has a rejection that is substantive other than the provisional double patenting rejection, and is therefore, maintained. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The

Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m. The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Primary Examiner in charge of the prosecution, Dr. Kenneth Horlick, can be reached at (571) 272-0784. If the attempts to reach the above Examiners are unsuccessful, the Examiner's supervisor, Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Patent Examiner
Art Unit 1637
2/23/05

YOUNG J. KIM
PATENT EXAMINER

yjk